WEST Search History

DATE: Wednesday, July 03, 2002

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=OR			
L19	L1 and L2 and L16	2	L19
L18	L1 and L2 and L17	2	L18
L17	cpt-11	297	L17
L16	irinotecan	284	L16
L15	L1 and L2 and L14	5	L15
L14	fludarabine	397	L14
L13	L1 and L2 and L12	2	L13
L12	docetaxel	457	L12
L11	L1 and L2 and l10	32	L11
L10	paclitaxel	1604	L10
L9	genasense	0	L9
L8	gc3139	0	L8
L7	genta	600	L7
L6	augmerosen	0	L6
L5	g3139	11	L5
L4	L1 and L2 and L3	598	L4
L3	cancer therapeutic	227640	L3
L2	antisense	21777	L2
L1	bcl-2	1216	L1

END OF SEARCH HISTORY

L15 ANSWER 1 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:22172 BIOSIS
DOCUMENT NUMBER: PREV200200022172
TITLE: G3139 downregulates the expression of **bcl-2** in patients with metastatic colorectal cancer treated with **irinotecan** (CPT-11.
AUTHOR(S): Ochoa, L. (1); Kuhn, J.; Salinas, R.; Hammond, L.; Hao, D.; Rodriguez, G.; Smith, L.; Berg, K.; Schwartz, G.; Patnaik, A.; Zwiebel, J.; Fingert, H.; Rowinsky, E. K.; Tolcher, A. W.
CORPORATE SOURCE: (1) CTEP, NCI, Rockville, MD USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2001) Vol. 42, pp. 848. print.
Meeting Info.: 92nd Annual Meeting of the American Association for Cancer Research New Orleans, LA, USA March 24-28, 2001
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L15 ANSWER 2 OF 7 MEDLINE
ACCESSION NUMBER: 2001045644 MEDLINE
DOCUMENT NUMBER: 20516024 PubMed ID: 11060696
TITLE: Therapeutic advances in small cell lung cancer.
AUTHOR: Worden F P; Kalemkerian G P
CORPORATE SOURCE: University of Michigan Cancer Center, 1366 Cancer Center - 09221500 E. Medical Center Dr., Ann Arbor, MI 48109-0922, USA.
SOURCE: EXPERT OPINION ON INVESTIGATIONAL DRUGS, (2000 Mar) 9 (3) 565-79. Ref: 108
Journal code: 9434197. ISSN: 1354-3784.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001204

AB Small cell lung cancer (SCLC) is characterised by neuroendocrine differentiation, early metastatic potential and initial responsiveness to cytotoxic therapy. Unfortunately, despite recent therapeutic advances, most patients relapse and the overall five-year survival rate is only 5%. Standard treatment of SCLC consists of platinum-based combination chemotherapy, with thoracic irradiation added for patients with limited-stage disease. Several newer chemotherapeutic drugs have recently been shown to have significant activity in patients with untreated or relapsed SCLC. These agents include: the topoisomerase I inhibitors, topotecan and **irinotecan**; the taxanes, paclitaxel and docetaxel; the pyrimidine analogue, gemcitabine; and the vinca alkaloid, vinorelbine. Recent advances in our understanding of the molecular events involved in the pathogenesis and progression of SCLC have led to the identification of a variety of potential targets for novel therapeutic interventions. Strategies aimed at inhibiting the myriad of growth factor pathways that control the proliferation of SCLC cells, include: broad spectrum neuropeptide antagonists (e.g., substance P analogues); growth factor/receptor-specific inhibitors (e.g., anti-GRP monoclonal antibodies, bradykinin antagonist dimers); and a variety of selective protein kinase inhibitors. The importance of cell death pathways in carcinogenesis and treatment-resistance has led to several novel strategies targeting apoptotic mediators, such as **bcl-2**, that are frequently dysregulated in SCLC (e.g., **bcl-2**

antisense). Our current challenges are to further refine these promising therapeutic strategies, efficiently evaluate their activity in the clinical setting and integrate them into more effective treatment regimens to improve the overall prognosis of patients with SCLC.

L15 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:171627 CAPLUS
DOCUMENT NUMBER: 136:226776
TITLE: Methods of treatment of a **bcl-2** disorder using **bcl-2** **antisense** oligomers
INVENTOR(S): Warrel, Raymond P., Jr.; Klem, Robert E.; Fingert, Howard
PATENT ASSIGNEE(S): Genta Incorporated, USA
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002017852	A2	20020307	WO 2001-US26414	20010823

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

MY US Case

PRIORITY APPLN. INFO.:
US 2000-227970P P 20000825
US 2000-237009P P 20000929
US 2000-709170 A 20001110

AB The present invention is directed to the use of **bcl-2** **antisense** oligomers to treat and prevent **bcl-2** related disorders. These disorders include cancers, tumors, carcinomas and cell-proliferative related disorders. In one embodiment of the invention, a **bcl-2** **antisense** oligomer is administered at high doses. The present invention is also directed to a method of preventing or treating a **bcl-2** related disorder, in particular cancer, comprising administering a **bcl-2** **antisense** oligomer for short periods of time. The present invention is further drawn to the use of **bcl-2** **antisense** oligomers to increase the sensitivity of a subject to cancer therapeutics. The present invention also relates to pharmaceutical compns. comprising one or more **bcl-2** **antisense** oligomers, which may comprise one or more cancer therapeutic agents.

L15 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:176432 CAPLUS
DOCUMENT NUMBER: 132:189223
TITLE: Therapeutic advances in small cell lung cancer
AUTHOR(S): Worden, Francis P.; Kalemkerian, Gregory P.
CORPORATE SOURCE: University of Michigan, Ann Arbor, MI, USA
SOURCE: Expert Opinion on Investigational Drugs (2000), 9(3), 565-579
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 108 refs. Small cell lung cancer (SCLC) is characterized by

neuroendocrine differentiation, early metastatic potential and initial responsiveness to cytotoxic therapy. Unfortunately, despite recent therapeutic advances, most patients relapse and the overall five-year survival rate is only 5%. Std. treatment of SCLC consists of platinum-based combination chemotherapy, with thoracic irradn. added for patients with limited-stage disease. Several newer chemotherapeutic drugs have recently been shown to have significant activity in patients with untreated or relapsed SCLC. These agents include: the topoisomerase I inhibitors, topotecan and **irinotecan**; the taxanes, paclitaxel and docetaxel; the pyrimidine analog, gemcitabine; and the vinca alkaloid, vinorelbine. Recent advances in our understanding of the mol. events involved in the pathogenesis and progression of SCLC have led to the identification of a variety of potential targets for novel therapeutic interventions. Strategies aimed at inhibiting the myriad of growth factor pathways that control the proliferation of SCLC cells, include: broad spectrum neuropeptide antagonists (e.g., substance P analogs); growth factor/receptor-specific inhibitors (e.g., anti-GRP monoclonal antibodies, bradykinin antagonist dimers); and a variety of selective protein kinase inhibitors. The importance of cell death pathways in carcinogenesis and treatment-resistance has led to several novel strategies targeting apoptotic mediators, such as **bcl-2**, that are frequently disregulated in SCLC (e.g., **bcl-2 antisense**). Our current challenges are to further refine these promising therapeutic strategies, efficiently evaluate their activity in the clin. setting and integrate them into more effective treatment regimens to improve the overall prognosis of patients with SCLC.

REFERENCE COUNT: 108 THERE ARE 108 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 5 OF 7 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2001200224 EMBASE

TITLE: Apoptosis modulators as cancer therapeutics.

AUTHOR: Penn L.Z.

CORPORATE SOURCE: Prof. L.Z. Penn, Ontario Cancer Institute, Princess Margaret Hospital, 610 University Avenue, Toronto, Ont. M5G 2M9, Canada. lpenn@oci.utoronto.ca

SOURCE: Current Opinion in Investigational Drugs, (2001) 2/5 (684-692).
Refs: 109
ISSN: 0967-8298 CODEN: CIDREE

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT:
016 Cancer
037 Drug Literature Index
030 Pharmacology
038 Adverse Reactions Titles
022 Human Genetics
029 Clinical Biochemistry
005 General Pathology and Pathological Anatomy

LANGUAGE: English

SUMMARY LANGUAGE: English

AB In the past ten years a wealth of fundamental knowledge delineating the molecular mechanism(s) of apoptosis has emerged, and can now be exploited to identify novel apoptotic modulators for the treatment of cancer. Two distinct yet complimentary classes of non-genotoxic agonists that can selectively kill tumor cells are discussed; agents that target 'clasical and 'atypical' apoptotic signaling pathways. The goal of agents targeting classical apoptosis and survival pathways is to directly modulate key apoptotic regulators such as **Bcl-2**, Akt/PKB, and p53.
The aim of agents targeting atypical apoptotic pathways is to target signaling cascades whose inhibition remains non-lethal in normal cells, yet is suicidal in tumor cells. Such compounds presently under development include inhibitors of heat shock protein 90, histone deacetylases and

HMG-CoA reductase. Both classes of apoptotic modulators have merit and identification of additional agonists of this nature will provide the many diverse cytotoxic agents that are required to combat the many diseases we call cancer.

L15 ANSWER 6 OF 7 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000370319 EMBASE
TITLE: From bench to clinic with apoptosis-based therapeutic agents.
AUTHOR: Nicholson D.W.
CORPORATE SOURCE: D.W. Nicholson, Merck Frosst Ctr. Therapeut. Res., Merck Research Laboratories, PO 1005 Pointe Claire-Dorval, Quebec, Que. H9R 4P8, Canada
SOURCE: Nature, (12 Oct 2000) 407/6805 (810-816).
Refs: 63
ISSN: 0028-0836 CODEN: NATUAS
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
016 Cancer
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A retrospective look at the basis of human disease pathogenesis almost always reveals an apoptotic component that either contributes to disease progression or accounts for it. What makes this field particularly exciting is the breadth of therapeutic opportunities that are on offer. The pace of apoptosis research has raised expectations that therapeutics will follow soon. But many of the organizations that are best placed to take advantage of these discoveries consider the ability to modulate the life or death of a cell for the purpose of disease treatment as perhaps being 'too good to be true'. Nevertheless, practical therapeutics that modulate apoptosis will no doubt appear in the clinic or on the shelf in the next few years.

L15 ANSWER 7 OF 7 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000080933 EMBASE
TITLE: Therapeutic advances in small cell lung cancer.
AUTHOR: Worden F.P.; Kalemkerian G.P.
CORPORATE SOURCE: G.P. Kalemkerian, University of Michigan Cancer Center, 1366 Cancer Center-0922, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-0922, United States. kalemker@umich.edu
SOURCE: Expert Opinion on Investigational Drugs, (2000) 9/3 (565-579).
Refs: 108
ISSN: 1354-3784 CODEN: EOIDER
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Small cell lung cancer (SCLC) is characterised by neuroendocrine differentiation, early metastatic potential and initial responsiveness to cytotoxic therapy. Unfortunately, despite recent therapeutic advances, most patients relapse and the overall five-year survival rate is only 5%. Standard treatment of SCLC consists of platinum-based combination chemotherapy, with thoracic irradiation added for patients with limited-stage disease. Several newer chemotherapeutic drugs have recently been shown to have significant activity in patients with untreated or relapsed SCLC. These agents include: the topoisomerase I inhibitors,

topotecan and **irinotecan**; the taxanes, paclitaxel and docetaxel; the pyrimidine analogue, gemcitabine; and the vinca alkaloid, vinorelbine. Recent advances in our understanding of the molecular events involved in the pathogenesis and progression of SCLC have led to the identification of a variety of potential targets for novel therapeutic interventions. Strategies aimed at inhibiting the myriad of growth factor pathways that control the proliferation of SCLC cells, include: broad spectrum neuropeptide antagonists (e.g., substance P analogues); growth factor/receptor-specific inhibitors (e.g., anti-GRP monoclonal antibodies, bradykinin antagonist dimers); and a variety of selective protein kinase inhibitors. The importance of cell death pathways in carcinogenesis and treatment-resistance has led to several novel strategies targeting apoptotic mediators, such as **bcl-2**, that are frequently dysregulated in SCLC (e.g., **bcl-2 antisense**). Our current challenges are to further refine these promising therapeutic strategies, efficiently evaluate their activity in the clinical setting and integrate them into more effective treatment regimens to improve the overall prognosis of patients with SCLC.

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(FILE 'HOME' ENTERED AT 14:11:48 ON 03 JUL 2002)

FILE 'BIOSIS, MEDLINE, CAPLUS, EMBASE' ENTERED AT 14:11:59 ON 03 JUL 2002

L1	45632	BCL-2
L2	72365	ANTISENS?
L3	107	G3139
L4	10	AUGMEROSEN
L5	217	GENTA
L6	0	GC3139
L7	35	GENASENSE
L8	20954	PACLITAXEL
L9	5777	DOCETAXEL
L10	6088	FLUDARABINE
L11	5521	IRINOTECAN
L12	55	L1 AND L2 AND L8
L13	36	L1 AND L2 AND L9
L14	17	L1 AND L2 AND L10
L15	7	L1 AND L2 AND L11

=> d L14 ibib, abs 1-17

L14 ANSWER 1 OF 17 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:261492 BIOSIS
DOCUMENT NUMBER: PREV200200261492
TITLE: **Bcl-2 antisense** (GenasenseTM) induces apoptosis and potentiates activity of both cytotoxic chemotherapy and rituximab in primary CLL cells.
AUTHOR(S): Auer, Rebecca L. (1); Corbo, Maggie (1); Fegan, Christopher D.; Frankel, Stan R.; Cotter, Finbarr E. (1)
CORPORATE SOURCE: (1) Dept. Experimental Haematology, Bart's and London, London UK
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 808a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

AB Failure of treatment in CLL is often characterised by increased expression of the anti-apoptosis protein **Bcl-2**. High levels of **Bcl-2** protein block the apoptotic death machinery at the mitochondrial level by maintaining the permeability transition pore (PTP) in the closed position. This study aimed to investigate the response of primary CLL cells to down regulation of the **Bcl-2** protein by **Bcl-2** phosphorothioate **antisense** oligonucleotide (ASO) G3139 (GenasenseTM - Genta, USA). Primary CLL cells were obtained from peripheral blood and were selected by Ficoll separation followed by CD19 magnetic bead selection. **Bcl-2** expression was confirmed by immunohistochemistry. Short term liquid cultures in RPMI and 10% fetal calf serum were set up in microtitre format. All data sets were carried out in triplicate. Cells were treated optimally for 72 hours with ASO (2muM), or control sense or nonsense oligonucleotides. Consistent **Bcl-2** downregulation could be confirmed at 72 hr. Various doses of rituximab and dexamethasone were added to the culture. Assessment of the mitochondrial PTP response (JC-1, DiOC6) and apoptosis (cell membrane MC540) were then performed by flow analysis at 4, 24 and 48 hours. The cells treated with Genasense alone showed marked and highly significant apoptotic responses maximal at 2muM ($p<0.0001$ MC540 and DiOC6 24 hours). This was more marked than responses seen in lymphoma cell lines (DoHH2 and SUD4). Control oligonucleotide treated cells remained unaffected. The single agent

activity of Genasense in this system was greater than **fludarabine** or cyclophosphamide. Cells subsequently treated in combination with rituximab (1, 1.5, 2.5, 5 mug/ml) showed enhanced response in combination with ASO in a dose response relationship. Similar potentiation was seen when ASO was added to dexamethasone (1muM) or **fludarabine** (50 muM). In summary, downregulation of **Bcl-2** protein by Genasense ASO alone shows considerable apoptotic effect in primary CLL cells at a concentration easily achieved in vivo without toxicity. Genasense was synergistic with rituximab. Genasense ASO alone or in combination with current therapies should produce an enhanced clinical response in patients with CLL.

L14 ANSWER 2 OF 17 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:261347 BIOSIS
DOCUMENT NUMBER: PREV200200261347
TITLE: **Bcl-2 antisense** (Genasense) as monotherapy for refractory chronic lymphocytic leukemia.
AUTHOR(S): O'Brien, Susan (1); Giles, Francis (1); Rai, Kanti; Andreeff, Michael (1); Cunningham, Casey; Frankel, Stanley; Keating, Michael (1)
CORPORATE SOURCE: (1) Leukemia, M.D. Anderson Cancer Center, Houston, TX USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 772a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

AB Wild-type **Bcl-2** protein is normally found within the bilaminar membrane of the mitochondrion, where it is believed to negatively regulate the release of cytochrome C into the cytoplasm after an apoptotic signal has triggered dimerization of bax protein. Thus, high levels of **Bcl-2** decrease apoptosis by preventing or slowing downstream activation of caspases via cytochrome C. Preclinical studies have shown that **antisense**-mediated reduction of **Bcl-2** consistently amplifies the cytotoxic activity of many chemotherapeutic agents across a broad range of hematologic malignancies and solid tumors. However, homologous recombination has generated a murine **Bcl-2** -/- knockout that displays profound immunodeficiency due to lymphoid hypoplasia, suggesting that presence of **Bcl-2** itself is an essential viability factor for lymphoid cells. **Bcl-2** is commonly over-expressed in CLL cells, and recent in vitro data indicate that **antisense**-mediated reduction of **Bcl-2** protein directly induces apoptosis of CLL cells in the absence of other agents. Therefore, concurrently with a randomized trial that uses **Bcl-2 antisense** (Genasense) combined with **fludarabine**/cyclophosphamide, we initiated a clinical study to evaluate its pharmacokinetics in CLL patients (pts), biokinetics of **Bcl-2** protein down-regulation and re-expression in CLL cells, and to examine whether this drug exhibited single-agent activity independent of its chemosensitizing effects. To date, 6 pts have been treated with **Bcl-2 antisense** administered as a continuous IV infusion at doses ranging from 3 to 7 mg/kg/day for 5 to 7 days every 3 wks. At the 5 and 7 mg/kg/d dose levels, 4 pts experienced high fever; 2 pts had severe hypotension and hypoglycemia requiring ICU admission. One pt developed transient acral cyanosis due to development of a cold agglutinin during the 1st course, and 1 pt developed severe sacral pain and a Coombs-positive hemolytic anemia during the 2nd course. All 6 pts achieved reduction of peripheral leukocytosis, one of whom had tumor lysis syndrome. In summary, unlike pts with solid tumors who routinely tolerate doses of 7 mg/kg/d (but similar to pts with non-Hodgkin's lymphoma), pts with CLL appear markedly more sensitive to **Bcl-**

2 antisense. Whether this decreased tolerance is due to the differing biology of **Bcl-2** in lymphoid cells is unclear. Because of these reactions, all current studies in CLL have reduced the initial drug dose to 3 mg/kg/d, used prednisone (10 mg/dX3d) to ameliorate early febrile response, and employed appropriate phophylaxis against tumor lysis. **Bcl-2 antisense** may exert single-agent activity in CLL that does not depend upon chemosensitization to other cytotoxic drugs.

L14 ANSWER 3 OF 17 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:152288 BIOSIS
DOCUMENT NUMBER: PREV200200152288
TITLE: Clinical and biological activity of GenasenseTM (G3139, Genta, Inc.) (GS), a **bcl-2 antisense**, in refractory (REF) or relapsed (REL) acute leukemia (AL): A phase I study.
AUTHOR(S): Marcucci, Guido (1); Byrd, John C. (1); Cataland, Spero R. (1); Fisher, Diane B. (1); Lucas, David (1); Chan, Kenneth K. (1); Klisovic, Marko (1); Young, Donn C. (1); Didier, Lisa A. (1); Balcerzak, Stanley P. (1); Frankel, Stanley R.; Kraut, Eric H. (1); Bloomfield, Clara D. (1); Grever, Michael R. (1); Caligiuri, Michael A. (1)
CORPORATE SOURCE: (1) Comprehensive Cancer Center, Ohio State University, Columbus, OH USA
SOURCE: Blood, (November 16, 2001) Vol. 98, No. 11 Part 2, pp. 216b. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 2 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

AB Overexpression of **bcl-2**, an inhibitor of cell apoptosis, is a potential mechanism for chemoresistance in AL, and is associated with unfavorable prognosis. Chemotherapy-induced apoptosis may be enhanced by **bcl-2** downregulation. GS (Genta, Inc.) is an 18-mer phosphorothioate **bcl-2 antisense** that downregulates **bcl-2** expression in vitro and in vivo. Here, we report a Phase I dose escalation study in patients (pts) with REF or REL AL treated with GS in combination with **fludarabine** (FL), cytarabine (ARA-C (A)), and G-CSF (FLAG). Disease response was assessed utilizing the NCI criteria for AL. Of the 20 pts enrolled in this study, 9 (45%) had disease response, 5 AML and 2 ALL with complete remission (CR), and 2 AML with no evidence of disease (NED) but failure to recover normal neutrophil and/or platelet counts. Of the 9 responders, 4 were >60 years of age, 2 had primary REF disease, 5 had relapsed following previous high-dose ARA-C (HiDAC), and 1 following autologous stem cell transplant (SCT). Of the 9 responders, 2 continue in CR at d439 and 309, 1 is with NED at d86 and 1 died with NED at d94 post alloSCT. Side effects with this combination included fever, nausea, emesis, hypocalcemia, hypophosphatemia and fluid retention. These were manageable, non-dose limiting toxicities and not clearly attributable to GS. One of 6 pts entered at dose level 5 experienced CNS bleeding at d9. Median time of neutrophil recovery from start of FL and A chemotherapy (d6) was 23 days (range 8 to 38 days); median time for platelet recovery (>50,000) was 39 days (range 21 to 56 days). Four pts who achieved CR at drug levels 1, 2, 3 and 5, received a second treatment course. Of the 4, 1 pt (dose level 5) experienced grade 4 infection (i.e., septic shock), elevated liver function tests and delayed count recovery. Pharmacokinetic (PK) analysis at the first three dose levels showed no significant differences in the GS plasma levels between responders and non-responders. **Bcl-2** mRNA levels were measured at baseline, d3 and d5 in blood by Real Time RT-PCR. Of 14 pts analyzed, 9 had **bcl-2** reduction (2.4 to 71%); 5 pts, including 2 responders, had **bcl-**

2 increase (41-163%). There was no difference in **bcl-2** levels in pts treated with 4 versus 7 mg/kg/d GS. In 3 pts, changes in **bcl-2** protein levels measured by immunoblotting were compared, and found consistent with the RT-PCR results. Completion of **bcl-2** mRNA and protein quantification in bone marrow (BM) and blood, and correlation with PK and clinical results are underway. This study suggests that the use of GS in combination with chemotherapy in REL/REF AL is feasible. The response rate of 45% in this poor-risk population is encouraging. These results, therefore, support the expanded use of GS in poor-risk AL.

L14 ANSWER 4 OF 17 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:314080 BIOSIS
DOCUMENT NUMBER: PREV200100314080
TITLE: Differentially expressed genes in B-chronic lymphocytic leukemia: Evidence that manipulation of **Bcl-2** gene leads to increased killing of CLL cells.
AUTHOR(S): Vu, Uyen E. (1); Dickinson, John (1); Wang, Peng (1); Wang, Xiaojun (1); Kelly, David L. (1); Rizzino, Angie A. (1); Pavletic, Steven Z. (1); Joshi, Shantaram S. (1)
CORPORATE SOURCE: (1) University of Nebraska Medical Center, Omaha, NE USA
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 714a-715a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Defective apoptosis machinery and resistance to killing by chemotherapeutic agents as well as by cytotoxic effector cells are some of the major features of B-chronic lymphocytic leukemia (B-CLL). Identification and subsequent manipulation of the genes responsible for the therapy resistant behavior of CLL cells may lead to their increased killing. Therefore, in this study, we have investigated the differential expression of cell cycle/apoptosis associated genes in CLL using an immortal cell line, WSU-CLL and RT-PCR and/or cDNA array analyses. The results were compared to Raji, Burkitt lymphoma, and K562, chronic myelogenous leukemia cell lines. The differentially expressed genes include elevated expression of **Bcl-2**, DAD-1, cyclin D3 and cyclin dependent kinase 4 inhibitor D and lower expression of Bax and CDC25B. Subsequently, cDNA array analysis of leukemic cells from six CLL patients confirmed the differential expression of some of these genes including **Bcl-2** over expression. Therefore in an attempt to target the differentially expressed genes, **Bcl-2** was down-regulated using **Bcl-2** **antisense** oligonucleotide in CLL cells. The **Bcl-2** down regulated CLL cells were more susceptible to killing by chemotherapeutic agent **fludarabine** as well as by IL-2 activated effector cells as determined by MTT assay and in vitro cytotoxicity assays respectively. Thus, these results suggest that alterations in certain cell cycle/apoptosis genes might play important roles in the resistance behavior of CLL cells. In addition, these findings also demonstrate that cytotoxicity to CLL can be enhanced by targeting the differentially expressed genes.

L14 ANSWER 5 OF 17 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:293774 BIOSIS
DOCUMENT NUMBER: PREV200100293774
TITLE: Phase I trial of GenasenseTM (G3139, GENTA, INC.), a **BCL-2 antisense** (AS), in refractory (REF) or relapsed (REL) acute leukemia (AL.
AUTHOR(S): Marcucci, G. (1); Bloomfield, C. D. (1); Balcerzak, S. P.

(1); Kourlas, P. J. (1); Stanley, H. R. (1); Fingert, H.; Maghraby, E. A. (1); Lucas, D. (1); Chen, K. K. (1); Byrd, J. C. (1); Kraut, E. H. (1); Grever, M. R. (1); Caligiuri, M. A. (1)

CORPORATE SOURCE: (1) The Comprehensive Cancer Center, The Ohio State University, Columbus, OH USA

SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 119a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.

DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In AL a strong association between chemotherapy resistance and overexpression of **BCL-2** exists. We hypothesized that chemotherapy-induced apoptosis is enhanced by **BCL-2** downregulation. G3139 is a **BCL-2** AS that downregulates **BCL-2** expression in vitro and in vivo. We report on 10 pts enrolled at levels 1-3 of a Phase I study with G3139 + **fludarabine**, ARA-C, and G-CSF (FLAG) therapy for REF/REL AL. G3139 (4mg/kg/day) is given on d1-10, whereas both **fludarabine** (starting @ 15mg/m2) and ARA-C (starting @ 1000 mg/m2) are given on d6-10 and escalated in successive cohorts. Therapy-related fever, nausea, emesis, hypocalcemia, hypophosphatemia, and fluid retention were not dose-limiting. Hematologic toxicities were as expected. Steady state G3139 plasma levels exceeding the relevant target level (1mug/ml) were achieved after 24h. Quantification of **BCL-2** levels in AL blasts will be presented. Three pts achieved CR and received a 2nd course of therapy, two continue with NED at d53 and 111. Two pts had NED but persistent neutropenia/thrombocytopenia at d52 and 55; one of them continues with NED at d76. Three of 5 responders had prior HDAC. One patient had leukostasis at d6, and was taken off study. The data suggest that G3139 is feasible for addition to multicycle cycle induction regimens for AL; moreover the encouraging 50% response rate-including pts with REF AL and prior HDAC - supports further development of G3139 of G3139 in combination regimens for REL/REF AL.

L14 ANSWER 6 OF 17 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:428604 BIOSIS
DOCUMENT NUMBER: PREV199900428604
TITLE: Induction of apoptosis and differentiation by **fludarabine** in human leukemia cells (U937): Interactions with the macrocyclic lactone bryostatin 1.

AUTHOR(S): Vrana, J. A.; Wang, Z.; Rao, A. S.; Tang, L.; Chen, J.-H.; Kramer, L. B.; Grant, S. (1)

CORPORATE SOURCE: (1) Division of Hematology/Oncology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA, 23298 USA

SOURCE: Leukemia (Basingstoke), (July, 1999) Vol. 13, No. 7, pp. 1046-1055.
ISSN: 0887-6924.

DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We have examined interactions between the purine nucleoside analog **fludarabine** (9-beta-arabinofuranosyl-2-fluoroadenine) and the macrocyclic lactone bryostatin 1 in the human monocytic leukemic cell line U937. **Fludarabine** exerted dose-dependent effects on U937 cell viability and growth which were associated with both induction of apoptosis, as well as cellular maturation. Incubation of cells with bryostatin 1 (10 nM; 24 h) after, but not before a 6-h exposure to 10 muM **fludarabine** resulted in a modest but significant increase in

apoptosis, and was associated with greater than a 1 log reduction in clonogenicity. Subsequent exposure to bryostatin 1 also increased the percentage of **fludarabine**-treated cells displaying differentiation-related features (eg plastic adherence, CD11b positivity) compared to cells exposed to **fludarabine** alone. Bryostatin 1 did not increase the retention of the active **fludarabine** metabolite, F-ara-ATP, nor did it increase 3H-F-ara-A incorporation into DNA. Despite its capacity to trigger cellular maturation, **fludarabine** exposure (either with or without bryostatin 1) failed to induce the cyclin-dependent kinase inhibitors (CDKIs) p21WAFI/CIP1 and p27KIP1. Nevertheless, dysregulation of p21 (resulting from stable transfection of cells with a p21WAFI/CIP1 **antisense** construct) reduced **fludarabine**-mediated differentiation, while inducing a corresponding increase in apoptosis. Enforced expression of **Bcl-2** partially protected cells from **fludarabine**-related apoptosis, an effect that was overcome, in part, by subsequent exposure of cells to bryostatin 1. Interestingly, **Bcl-2** -overexpressing cells were as or in some cases, more susceptible to differentiation induction by **fludarabine** (+- bryostatin 1) than their empty vector-containing counterparts. Collectively, these results indicate that the antiproliferative effects of **fludarabine** toward U937 leukemic cells involve both induction of apoptosis and cellular maturation, and that each of these processes may be enhanced by bryostatin 1.

L14 ANSWER 7 OF 17 MEDLINE
ACCESSION NUMBER: 2001536995 MEDLINE
DOCUMENT NUMBER: 21240485 PubMed ID: 11342340
TITLE: Increased cytotoxicity against B-chronic lymphocytic leukemia by cellular manipulations: potentials for therapeutic use.
AUTHOR: Vu U E; Pavletic Z S; Wang X; Joshi S S
CORPORATE SOURCE: Department of Cell Biology and Anatomy, University of Nebraska Medical Center Omaha, Nebraska 68198-6395, USA.
SOURCE: LEUKEMIA AND LYMPHOMA, (2000 Nov) 39 (5-6) 573-82. Journal code: 9007422. ISSN: 1042-8194.
PUB. COUNTRY: Switzerland
LANGUAGE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: English
ENTRY MONTH: Priority Journals
ENTRY DATE: 200110
Entered STN: 20011008
Last Updated on STN: 20011008
Entered Medline: 20011004

AB B-cell chronic lymphocytic leukemia (CLL) is characterized by profound immune dysfunction and a marked resistance to apoptosis. Understanding the cellular biology of immune effector cells from CLL patients as well as leukemic target cells is essential to developing immune mediated therapeutic strategies for CLL. In this study, an immortal CLL cell line called WSU-CLL has been used to study the characteristics of B-cell CLL as a tumor target for natural killer (NK), activated natural killer, and lymphokine activated killer (LAK) cells. The WSU-CLL cells were significantly less ($p<0.001$) susceptible to NK cell mediated cytotoxicity compared to K562, a standard tumor target cell line. In vitro activation of effector cells with either short term, low dose IL-2 or long term, high dose IL-2 significantly increased the susceptibility of CLL cells for cell mediated killing. The addition of CD1a+/CD3-/CD4+/CD80+/CD83+ dendritic cells derived from human umbilical cord blood increased the cytotoxicity of LAK cells against WSU-CLL. There is an increased expression of **Bcl-2** and decreased expression of Fas on WSU-CLL cells as determined by RT-PCR techniques indicating possible roles for these genes in exerting resistance to immune cell mediated lysis. When **Bcl-2** expression was downregulated in WSU-CLL cells using gene specific **antisense** oligonucleotides, the

susceptibility of WSU-CLL cells to the cytotoxicity of chemotherapeutic agent **Fludarabine** was increased. Thus, our results suggest that in vitro activation with cytokines, addition of accessory cell populations such as dendritic cells and/or manipulation of key gene expression i.e. down regulation of **Bcl-2** might be potential strategies to increase the antitumor cytotoxicity against CLL cells.

L14 ANSWER 8 OF 17 MEDLINE
ACCESSION NUMBER: 1999326007 MEDLINE
DOCUMENT NUMBER: 99326007 PubMed ID: 10400420
TITLE: Induction of apoptosis and differentiation by **fludarabine** in human leukemia cells (U937): interactions with the macrocyclic lactone bryostatin 1.
AUTHOR: Vrana J A; Wang Z; Rao A S; Tang L; Chen J H; Kramer L B; Grant S
CORPORATE SOURCE: Department of Medicine, Medical College of Virginia, Virginia Commonwealth University, Richmond 23298, USA.
CONTRACT NUMBER: CA 63753 (NCI)
CA77141 (NCI)
SOURCE: LEUKEMIA, (1999 Jul) 13 (7) 1046-55.
Journal code: 8704895. ISSN: 0887-6924.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 19990806
Last Updated on STN: 19990806
Entered Medline: 19990726

AB We have examined interactions between the purine nucleoside analog **fludarabine** (9-beta-arabinofuranosyl-2-fluoroadenine) and the macrocyclic lactone bryostatin 1 in the human monocytic leukemic cell line U937. **Fludarabine** exerted dose-dependent effects on U937 cell viability and growth which were associated with both induction of apoptosis, as well as cellular maturation. Incubation of cells with bryostatin 1 (10 nM; 24 h) after, but not before a 6-h exposure to 10 microM **fludarabine** resulted in a modest but significant increase in apoptosis, and was associated with greater than a 1 log reduction in clonogenicity. Subsequent exposure to bryostatin 1 also increased the percentage of **fludarabine**-treated cells displaying differentiation-related features (eg plastic adherence, CD11b positivity) compared to cells exposed to **fludarabine** alone. Bryostatin 1 did not increase the retention of the active **fludarabine** metabolite, F-ara-ATP, nor did it increase 3H-F-ara-A incorporation into DNA. Despite its capacity to trigger cellular maturation, **fludarabine** exposure (either with or without bryostatin 1) failed to induce the cyclin-dependent kinase inhibitors (CDKIs) p21WAF1/CIP1 and p27KIP1. Nevertheless, dysregulation of p21 (resulting from stable transfection of cells with a p21WAF1/CIP1 **antisense** construct) reduced **fludarabine**-mediated differentiation, while inducing a corresponding increase in apoptosis. Enforced expression of **Bcl-2** partially protected cells from **fludarabine**-related apoptosis, an effect that was overcome, in part, by subsequent exposure of cells to bryostatin 1. Interestingly, **Bcl-2** -overexpressing cells were as or in some cases, more susceptible to differentiation induction by **fludarabine** (+/- bryostatin 1) than their empty vector-containing counterparts. Collectively, these results indicate that the antiproliferative effects of **fludarabine** toward U937 leukemic cells involve both induction of apoptosis and cellular maturation, and that each of these processes may be enhanced by bryostatin 1.

L14 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:171627 CAPLUS

DOCUMENT NUMBER: 136:226776
TITLE: Methods of treatment of a **bcl-2** disorder using **bcl-2** **antisense** oligomers
INVENTOR(S): Warrel, Raymond P., Jr.; Klem, Robert E.; Fingert, Howard
PATENT ASSIGNEE(S): Genta Incorporated, USA
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002017852	A2	20020307	WO 2001-US26414	20010823

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
US 2000-227970P P 20000825
US 2000-237009P P 20000929
US 2000-709170 A 20001110

AB The present invention is directed to the use of **bcl-2** **antisense** oligomers to treat and prevent **bcl-2** related disorders. These disorders include cancers, tumors, carcinomas and cell-proliferative related disorders. In one embodiment of the invention, a **bcl-2** **antisense** oligomer is administered at high doses. The present invention is also directed to a method of preventing or treating a **bcl-2** related disorder, in particular cancer, comprising administering a **bcl-2** **antisense** oligomer for short periods of time. The present invention is further drawn to the use of **bcl-2** **antisense** oligomers to increase the sensitivity of a subject to cancer therapeutics. The present invention also relates to pharmaceutical compns. comprising one or more **bcl-2** **antisense** oligomers, which may comprise one or more cancer therapeutic agents.

L14 ANSWER 10 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:128431 CAPLUS
DOCUMENT NUMBER: 135:136372
TITLE: Increased cytotoxicity against B-chronic lymphocytic leukemia by cellular manipulations: potentials for therapeutic use
AUTHOR(S): Vu, U. Eileen; Pavletic, Z. Steven; Wang, Xiaojun; Joshi, Shantaram S.
CORPORATE SOURCE: Departments of Cell Biology and Anatomy, University of Nebraska Medical Center, Omaha, NE, 68198-6395, USA
SOURCE: Leukemia & Lymphoma (2000), 39(5/6), 573-582
CODEN: LELYEA; ISSN: 1042-8194
PUBLISHER: Harwood Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB B-cell chronic lymphocytic leukemia (CLL) is characterized by profound immune dysfunction and a marked resistance to apoptosis. In this study, an immortal CLL cell line called WSU-CLL was used to study the characteristics of B-cell CLL as a tumor target for natural killer (NK), activated natural killer, and lymphokine-activated killer (LAK) cells.

The WSU-CLL cells were less susceptible to NK-cell-mediated cytotoxicity than K562, a std. tumor target cell line. In vitro activation of effector cells with either short-term, low-concn. interleukin-2 or long-term, high-concn. interleukin-2 increased the susceptibility of CLL cells to cell-mediated killing. The addn. of CD1a+/CD3-/CD4+/CD80+/CD83+ dendritic cells derived from human umbilical cord blood increased the cytotoxicity of LAK cells towards WSU-CLL. There was an increased expression of **Bcl-2** and decreased expression of Fas on WSU-CLL cells as detd. by RT-PCR techniques, indicating possible roles for these genes in exerting resistance to immune-cell-mediated lysis. When **Bcl-2** expression was downregulated in WSU-CLL cells by using gene-specific **antisense** oligonucleotides, the susceptibility of WSU-CLL cells to the cytotoxicity of the chemotherapeutic agent **fludarabine** was increased. Thus, the results suggest that in vitro activation with cytokines, addn. of accessory cell populations such as dendritic cells, and/or manipulation of key gene expression, i.e., downregulation of **Bcl-2**, might be potential strategies for increasing antitumor cytotoxicity to CLL cells.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:517819 CAPLUS

DOCUMENT NUMBER: 132:44513

TITLE: Induction of apoptosis and differentiation by **fludarabine** in human leukemia cells (U937): interactions with the macrocyclic lactone bryostatin 1

AUTHOR(S): Vrana, J. A.; Wang, Z.; Rao, A. S.; Tang, L.; Chen, J-H.; Kramer, L. B.; Grant, S.

CORPORATE SOURCE: Department of Medicine, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA, 23298, USA

SOURCE: Leukemia (1999), 13(7), 1046-1055
CODEN: LEUKED; ISSN: 0887-6924

PUBLISHER: Stockton Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The interactions between the purine nucleoside analog **fludarabine** (9-.beta.-arabinofuranosyl-2-fluoroadenine) and the macrocyclic lactone bryostatin 1 were examd. in the human monocytic leukemic cell line U937. **Fludarabine** exerted concn.-dependent effects on U937 cell viability and growth which were assocd. with both induction of apoptosis and cellular maturation. Incubation of cells with bryostatin 1 (10 nM; 24 h) after, but not before, a 6-h exposure to 10 .mu.M **fludarabine** resulted in a modest but significant increase in apoptosis and was assocd. with >1 log redn. in clonogenicity. Subsequent exposure to bryostatin 1 also increased the percentage of **fludarabine**-treated cells displaying differentiation-related features (e.g. plastic adherence, CD11b positivity) compared to cells exposed to **fludarabine** alone. Bryostatin 1 did not increase the retention of the active **fludarabine** metabolite, F-ara-ATP, nor did it increase [3H]F-ara-A incorporation into DNA. Despite its capacity to trigger cellular maturation, **fludarabine** exposure (either with or without bryostatin 1) failed to induce the cyclin-dependent kinase inhibitors (CDKIs) p21WAF1/CIP1 and p27KIP1. Nevertheless, dysregulation of p21 (resulting from stable transfection of cells with a p21WAF1/CIP1 **antisense** construct) reduced **fludarabine**-mediated differentiation, while inducing a corresponding increase in apoptosis. Enforced expression of **Bcl-2** partially protected cells from **fludarabine**-related apoptosis, an effect that was overcome, in part, by subsequent exposure of the cells to bryostatin 1. Interestingly, **Bcl-2**-overexpressing cells were as susceptible, or in some cases more susceptible, to differentiation induction by **fludarabine** (with or without bryostatin 1) than

their empty vector-contg. counterparts. These results indicate that the antiproliferative effects of **fludarabine** toward U937 leukemic cells involve both induction of apoptosis and cellular maturation, and that each of these processes may be enhanced by bryostatin 1.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 12 OF 17 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2002150963 EMBASE

TITLE: Trials with gemtuzumab ozogamicin (Mylotarg.RTM.) combined with chemotherapy regimens in acute myeloid leukemia.

AUTHOR: Stadtmauer E.A.

CORPORATE SOURCE: Dr. E.A. Stadtmauer, Univ. of Pennsylvania Cancer Center, 3400 Spruce Street, Philadelphia, PA 19104-4274, United States. edward.stadtmauer@uphs.upenn.edu

SOURCE: Clinical Lymphoma, (2002) 2/SUPPL.1 (S24-S28).
Refs: 13
ISSN: 1526-9655 CODEN: CLLYAO

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT:
016 Cancer
025 Hematology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Gemtuzumab ozogamicin (Mylotarg.RTM.) is an immunoconjugate composed of a recombinant humanized murine anti-CD33 antibody linked to calicheamicin, a potent cytotoxic agent. The aim of this review is to summarize ongoing trials with gemtuzumab ozogamicin in combination with chemotherapy in acute myeloid leukemia (AML) patients. The studies include determination of safety and efficacy of gemtuzumab ozogamicin in combination with chemotherapy in previously untreated as well as relapsed and refractory AML patients. These studies also determine gemtuzumab ozogamicin's activity in patients with other CD33(+) neoplastic diseases such as myelodysplastic syndrome, acute promyelocytic leukemia, chronic myeloid leukemia, and certain subsets of acute lymphocytic leukemia. Moreover, trials are exploring the use of gemtuzumab ozogamicin with novel targeted agents such as **Bcl-2 antisense** molecules.
Gemtuzumab ozogamicin is associated with an acceptable toxicity profile as a single agent; however, the incidence of veno-occlusive disease remains a concern with the use of gemtuzumab ozogamicin in combination with chemotherapy.

L14 ANSWER 13 OF 17 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2001164549 EMBASE

TITLE: Genasense Genta Inc.

AUTHOR: Banerjee D.

CORPORATE SOURCE: D. Banerjee, Memorial Sloan-Kettering Cancer Ctr., 1275 York Avenue, New York, NY 10021, United States. banerjee@aol.com

SOURCE: Current Opinion in Investigational Drugs, (2001) 2/4 (574-580).
Refs: 61
ISSN: 0967-8298 CODEN: CIDREE

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT:
037 Drug Literature Index
030 Pharmacology
016 Cancer
022 Human Genetics
038 Adverse Reactions Titles

LANGUAGE: English

L14 ANSWER 14 OF 17 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001071756 EMBASE
TITLE: Increased cytotoxicity against B-chronic lymphocytic leukemia by cellular manipulations: Potentials for therapeutic use.
AUTHOR: Vu U.E.; Pavletic Z.S.; Wang X.; Joshi S.S.
CORPORATE SOURCE: Dr. S.S. Joshi, Department of Cell Biology/Anatomy, Nebraska Medical Center University, Nebraska Medical Center Omaha, Omaha, NE 68198-6395, United States. ssjoshi@unmc.edu
SOURCE: Leukemia and Lymphoma, (2000) 39/5-6 (573-582). Refs: 29
ISSN: 1042-8194 CODEN: LELYEA
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB B-cell chronic lymphocytic leukemia (CLL) is characterized by profound immune dysfunction and a marked resistance to apoptosis. Understanding the cellular biology of immune effector cells from CLL patients as well as leukemic target cells in essential to developing immune mediated therapeutic strategies for CLL. In this study, an immortal CLL cell line called WSU-CLL has been used to study the characteristics of B-cell CLL as a tumor target for natural killer (NK), activated natural killer, and lymphokine activated killer (LAK) cells. The WSU-CLL cells were significantly less ($p<0.0001$) susceptible to NK cell mediated cytotoxicity compared to K562, a standard tumor target cell line. In vitro activation of effector cells with either short term, low dose IL-2 or long term, high dose IL-2 significantly increased the susceptibility of CLL cells for cell mediated killing. The addition of CD1a+/CD3-/CD4+/CD80+/CD83+ dendritic cells derived from human umbilical cord blood increased the cytotoxicity of LAK cells againts WSU-CLL. There is an increased expression of **Bcl-2** and decreased expression of Fas on WSU-CLL cells as determined by RT-PCR techniques indicating possible roles for these genes in exerting resistance to immune cell mediated lysis. When **Bcl-2** expression was downregulated in WSU-CLL cells using gene specific **antisense** oligonucleotides, the susceptibility of WSU-CLL cells to the cytotoxicity of chemotherapeutic agent **Fludarabine** was increased. Thus, our results suggests that in vitro activation with cytokines, addition of accesosry cell populations such as dendritic cells and/or manipulation of key gene expression i.e. down regulation of **Bcl-2** might be potential strategies to increase the antitumor cytotoxicity againts CLL cells.

L14 ANSWER 15 OF 17 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000370319 EMBASE
TITLE: From bench to clinic with apoptosis-based therapeutic agents.
AUTHOR: Nicholson D.W.
CORPORATE SOURCE: D.W. Nicholson, Merck Frosst Ctr. Therapeut. Res., Merck Research Laboratories, PO 1005 Pointe Claire-Dorval, Quebec, Que. H9R 4P8, Canada
SOURCE: Nature, (12 Oct 2000) 407/6805 (810-816). Refs: 63
ISSN: 0028-0836 CODEN: NATUAS
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology

016 Cancer
037 Drug Literature Index
039 Pharmacy

LANGUAGE: English
SUMMARY LANGUAGE: English

AB A retrospective look at the basis of human disease pathogenesis almost always reveals an apoptotic component that either contributes to disease progression or accounts for it. What makes this field particularly exciting is the breadth of therapeutic opportunities that are on offer. The pace of apoptosis research has raised expectations that therapeutics will follow soon. But many of the organizations that are best placed to take advantage of these discoveries consider the ability to modulate the life or death of a cell for the purpose of disease treatment as perhaps being 'too good to be true'. Nevertheless, practical therapeutics that modulate apoptosis will no doubt appear in the clinic or on the shelf in the next few years.

L14 ANSWER 16 OF 17 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999269462 EMBASE
TITLE: Induction of apoptosis and differentiation by **fludarabine** in human leukemia cells (U937): Interactions with the macrocyclic lactone bryostatin 1.
AUTHOR: Vrana J.A.; Wang Z.; Rao A.S.; Tang L.; Chen J.-H.; Kramer L.B.; Grant S.
CORPORATE SOURCE: S. Grant, Division of Hematology-Oncology, Medical College of Virginia, Virginia Commonwealth University, PO Box 980230, Richmond, VA 23298, United States
SOURCE: Leukemia, (1999) 13/7 (1046-1055).
Refs: 47
ISSN: 0887-6924 CODEN: LEUKED
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English

AB We have examined interactions between the purine nucleoside analog **fludarabine** (9-.beta.-arabinofuranosyl-2-fluoroadenine) and the macrocyclic lactone bryostatin 1 in the human monocytic leukemic cell line U937. **Fludarabine** exerted dose-dependent effects on U937 cell viability and growth which were associated with both induction of apoptosis, as well as cellular maturation. Incubation of cells with bryostatin 1 (10 nM; 24 h) after, but not before a 6-h exposure to 10 .mu.M **fludarabine** resulted in a modest but significant increase in apoptosis, and was associated with greater than a 1 log reduction in clonogenicity. Subsequent exposure to bryostatin 1 also increased the percentage of **fludarabine**-treated cells displaying differentiation-related features (eg plastic adherence, CD11b positivity) compared to cells exposed to **fludarabine** alone. Bryostatin 1 did not increase the retention of the active **fludarabine** metabolite, F-ara-ATP, nor did it increase 3H-F-ara-A incorporation into DNA. Despite its capacity to trigger cellular maturation, **fludarabine** exposure (either with or without bryostatin 1) failed to induce the cyclin-dependent kinase inhibitors (CDKIs) p21(WAF/CIP1) and p27(KIP1). Nevertheless, dysregulation of p21 (resulting from stable transfection of cells with a p21WAF/CIP1 an**tisense** construct) reduced **fludarabine**-mediated differentiation, while inducing a corresponding increase in apoptosis. Enforced expression of **Bcl-2** partially protected cells from **fludarabine**-related apoptosis, an effect that was overcome, in part, by subsequent exposure of cells to bryostatin 1. Interestingly, **Bcl-2** -overexpressing cells were as or in some cases, more susceptible to

differentiation induction by **fludarabine** (.+-. bryostatin 1) than their empty vector-containing counterparts. Collectively, these results indicate that the antiproliferative effects of **fludarabine** toward U937 leukemic cells involve both induction of apoptosis and cellular maturation, and that each of these processes may be enhanced by bryostatin 1.

L14 ANSWER 17 OF 17 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER:	1998237162 EMBASE
TITLE:	Introduction: Chronic lymphocytic leukemia in the purine analog era: New insights and challenges.
AUTHOR:	Cheson B.D.
CORPORATE SOURCE:	Dr. B.D. Cheson, 11028 Waycroft Way, North Bethesda, MD 20852, United States
SOURCE:	Seminars in Hematology, (1998) 35/3 SUPPL. 3 (1-2). ISSN: 0037-1963 CODEN: SEHEA3
COUNTRY:	United States
DOCUMENT TYPE:	Journal; Note
FILE SEGMENT:	016 Cancer 025 Hematology 037 Drug Literature Index
LANGUAGE:	English